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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Cancer- and Chemotherapy-Induced Anemia

Version 2.2011

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NCCN Guidelines™ Version 2.2011 Panel Members
Cancer- and Chemotherapy-Induced Anemia

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Discussion, References

* George M. Rodgers, III, MD, PhD/Chair ‡
Huntsman Cancer Institute at the University of Utah

* Pamela Sue Becker, MD, PhD ‡ Þ
University of Washington Medical Center/ Seattle Cancer Care Alliance

Charles L. Bennett, MD, PhD, MPP ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

David Cella, PhD θ
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Asher Chanan-Khan, MD †
Roswell Park Cancer Institute

Charles Cleeland, PhD θ
The University of Texas MD Anderson Cancer Center

Peter F. Coccia, MD ‡ €
UNMC Eppley Cancer Center at The Nebraska Medical Center

Benjamin Djulbegovic, MD, PhD † ‡ ξ
H. Lee Moffitt Cancer Center & Research Institute

Jeffrey A. Gilreath, PharmD б
Huntsman Cancer Institute at the University of Utah

Eric H. Kraut, MD ‡
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Ursula Matulonis, MD †
Dana-Farber/Brigham and Women's Cancer Center

Michael Millenson, MD ‡ Þ
Fox Chase Cancer Center

Denise Reinke, APRN, BC, AOCN #
University of Michigan Comprehensive Cancer Center

Joseph Rosenthal, MD ‡ €
City of Hope Comprehensive Cancer Center

Rowena N. Schwartz, PharmD б
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Richard S. Stein, MD ‡ ξ
Vanderbilt-Ingram Cancer Center

Gordana Vlahovic, MD †
Duke Comprehensive Cancer Center

Alva B. Weir III, MD ‡
St. Jude Children's Research Hospital/University of Tennessee Cancer Institute

NCCN
Mary Dwyer, MS
Maria Ho, PhD

‡ Hematology/Hematology oncology
θ Psychiatry/Psychology
† Medical oncology
€ Pediatric oncology
ξ Bone marrow transplantation
Þ Internal medicine
Nursing
б Pharmacotherapy
* Writing Committee Member

NCCN Guidelines Panel Disclosures

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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 2.2011 Updates Cancer- and Chemotherapy-Induced Anemia

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The 2.2011 version of the Cancer- and Chemotherapy-Induced Anemia Guidelines represents the addition of the updated Discussion.

Updates in the 1.2011 Version of the Cancer- and Chemotherapy-Induced Anemia Guidelines from the 2.2010 Version include:

General

- **The Cancer- and Chemotherapy-Induced Anemia Guidelines have been extensively revised to include indications for initial transfusion for patients with anemia of inflammation or anemia due to myelosuppressive chemotherapy for lymphoid malignancies and solid tumors and special categories for considering ESA use.**

ANEM-1

- **If hemoglobin (Hb) is ≤ 11 g/dL or ≥ 2 g/dL below baseline, an evaluation for possible causes of the anemia is suggested. If the cause is identified, the anemia is treated as indicated. If a cause is not identified, then anemia of inflammation or anemia due to myelosuppressive chemotherapy is considered.**

ANEM-2

- **Anemia of inflammation or anemia due to myelosuppressive chemotherapy for lymphoid malignancies and solid tumors, the risk assessment and indications for initial transfusion for "asymptomatic without significant comorbidities," and "asymptomatic with comorbidities or high risk" and "symptomatic" are new to the guidelines.**

ANEM-3

- **A new page titled, "Special categories in considering ESA use" which includes the following was added.**
  - **Cancer and chronic kidney disease (moderate to severe)**
  - **Myelosuppressive chemotherapy with curative intent**
  - **Patient undergoing palliative treatment**
  - **Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia**

ANEM-4

- **The "management of functional iron deficiency in patients receiving ESAs" is new to the guidelines.**

ANEM-A

- **"Indications for Red Blood Cell Transfusion in Cancer Patients" is new to the guidelines.**

ANEM-B 1 of 5

- **Titration for response, the second bullet was updated to correspond with the epoetin alfa and darbepoetin alfa prescribing information.**
  - **If Hb reaches a level needed to avoid transfusion or increases > 1 g/dL in any 2-week period, reduce dose by 25% for epoetin alfa and by 40% for darbepoetin alfa.**

ANEM-B 3 of 5

- **Cancer Patient Survival**
  - **Bullet 2 was modified by adding, "*While* three meta-analysis updates on survival *have indicated* an increased mortality risk with the use of ESAs, *two meta-analyses have indicated that ESAs use did not significantly affect mortality or disease progression".***
- **Thrombosis, a new bullet, "A clinical trial in chronic kidney disease patients demonstrated an increased risk of stroke with darbepoetin alfa" was added.**

ANEM-C

- **"REMS: Risk Evaluation and Mitigation Strategy For Erythropoiesis-stimulating Agents (ESAs)" is new to the guidelines.**

ANEM-D

- **Risks of the use of red blood cell transfusion: "increased thrombotic events" was added as an example.**

ANEM-E 1 of 3

- **Last bullet was modified, "Patients with active infection should not receive IV iron therapy."**

ANEM-E 2 of 3

- **Iron dextran, bullet "Repeated dosing once weekly for 10 doses to achieve total dose of 1 g" was added.**
- **Ferric gluconate, added alternate dosing "200 mg IV over 3-4 hrs, repeated every 3 weeks for 5 doses." In addition, two bullets were added "Individual doses above 200 mg are not recommended" and "Maximum total dose = 1000 mg."**
- **Iron sucrose dosage was modified, "200 mg IV *over 2-5 min, repeated dosing given every 1-4 weeks.* In addition, two bullets were added "Individual doses above 300 mg are not recommended" and "Maximum total dose = 1000 mg."**

UPDATES

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EVALUATION OF ANEMIA[a,b,c]

Hemoglobin (Hb) ≤ 11 g/dL or ≥ 2 g/dL below baseline →
- CBC with indices
- Blood smear morphology

→ **Evaluate anemia for possible cause as indicated:**
- First check
  - Reticulocyte count and MCV
- Then consider
  - Hemorrhage (stool guaiac, endoscopy)
  - Hemolysis (Coombs test, DIC panel, haptoglobin)
  - Nutritional (iron, total iron binding capacity, ferritin,[d] B12, folate)
  - Inherited (prior history, family history)
  - Renal (GFR < 60, low Epo)
  - Radiation-induced myelosuppression

→ **Treat as indicated**

→ **No cause identified** → **Consider anemia of inflammation or anemia due to myelosuppressive chemotherapy** → **See ANEM-2**

Myelodysplastic syndromes → **See NCCN Myelodysplastic Syndromes Guidelines**

Myeloid malignancies or ALL →
Treat underlying disease per NCCN guideline
See NCCN Guidelines Table of Contents
or
Appropriate therapy for Acute Lymphoblastic Leukemia (ALL)

[a] The NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines were formulated in reference to adult patients.
[b] Transplant-related anemia is not included.
[c] This is a basic evaluation for possible causes of anemia.
[d] If absolute iron deficiency is present (ferritin < 30 ng/mL and transferrin saturation < 15%), consider IV or oral iron supplementation. If hemoglobin increases after 4 wks then observe with periodic re-evaluation for symptoms and risk factors, if hemoglobin does not increase after 4 wks, see functional iron deficiency pathway (See ANEM-4).

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RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION

Anemia of inflammation or anemia due to myelosuppressive chemotherapy for lymphoid malignancies and solid tumors

- **Asymptomatic without significant comorbidities[e]** → **Observe** → **Periodic re-evaluation**
- **Asymptomatic with comorbidities[e] or high risk**
  - **Comorbidities:**
    - Cardiac including congestive heart failure and coronary heart disease
    - Chronic pulmonary disease
    - Cerebral vascular disease
  - **High risk:**
    - Progressive decline in hemoglobin with recent intensive chemotherapy or radiation

  → **Consider red blood cell transfusion per guidelines See Indications for Red Blood Cell Transfusion in Cancer Patients (ANEM-A)**
- **Symptomatic**
  - **Physiological:**
    - Sustained tachycardia, tachypnea, chest pain, dyspnea on exertion, lightheadedness, syncope, severe fatigue[f] preventing work and usual activity

  → **Red blood cell transfusion per guidelines See Indications for Red Blood Cell Transfusion in Cancer Patients (ANEM-A)**

See Special Categories in Considering ESA Use (ANEM-3)

[e] Degree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating red blood cell transfusion.
[f] Fatigue (FACT-F) and Anemia (FACT-An) subscales of the Functional Assessment of Cancer Therapy (FACT) and Brief Fatigue Inventory (BFI) are examples of standardized measures for assessing patient-reported fatigue.

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SPECIAL CATEGORIES IN CONSIDERING ESA USE

- **Cancer and chronic kidney disease (moderate to severe)** → **Consider treatment with ESAs by FDA indications/dosing/dosing adjustments for chronic kidney disease, under REMS guidelines, with informed consent of patient[h,i,j,k]** → **See Management of Functional Iron Deficiency in Patients Receiving ESAs (ANEM-4)**

- **Myelosuppressive chemotherapy with curative intent[g]**
  - **Examples of cancers for which there is therapy with curative intent: early stage breast cancer, Hodgkin lymphoma, non-Hodgkin's lymphoma, testicular cancer, early stage non-small cell lung cancer, etc.**

  → **ESAs not recommended**

- **Patient undergoing palliative treatment[l]** → **Consider treatment with ESAs by FDA indications/dosing/dosing adjustments, under REMS guidelines, with informed consent of patient[h,i,j]** → **See Management of Functional Iron Deficiency in Patients Receiving ESAs (ANEM-4)**
  or
  Consider red blood cell transfusion per guidelines (See ANEM-A)

- **Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia[l]** → **Consider red blood cell transfusion per guidelines (See ANEM-A)**
  or
  Clinical trial
  or
  Consider treatment with ESAs by FDA indications/dosing/dosing adjustments, under REMS guidelines, with informed consent of patient[h,i,j] → **See Management of Functional Iron Deficiency in Patients Receiving ESAs (ANEM-4)**

[g] A few studies suggest patients with small cell lung cancer on myelosuppressive chemotherapy may not have an increase in mortality when receiving ESAs. Oncologic Drugs Advisory Committee March 2008; Pirker et al. J Clin Oncol 2008; 26:2342-3249; Grote et al. J Clin Oncol 2005;23:9377-9386.

[h] See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (ANEM-B)

[i] Healthcare providers prescribing ESAs need to enroll in the ESA APPRISE program. See REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis Stimulating Agents (ESAs) (ANEM-C).

[j] Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. (See NCCN Venous Thromboembolic Disease Guidelines).

[k] The hemoglobin threshold for treatment and dosing with ESAs is different for chemotherapy-induced anemia and chronic kidney disease.

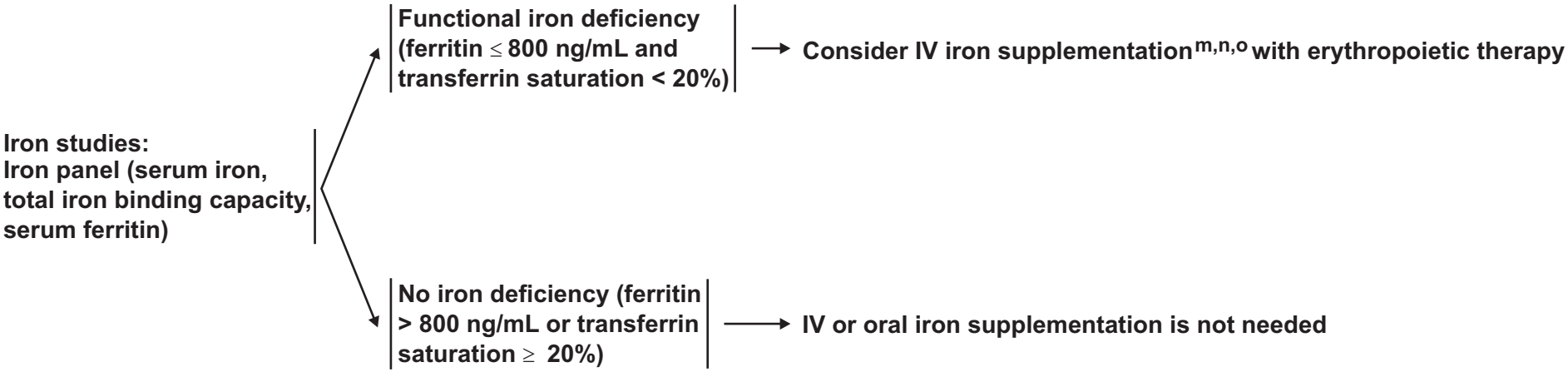
[l] See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion (ANEM-D).

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MANAGEMENT OF FUNCTIONAL IRON DEFICIENCY IN PATIENTS RECEIVING ESAs



See Parenteral Iron Preparations (ANEM-E)

[m] IV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. See Parenteral Iron Preparations (ANEM-E).

[n] Five randomized trials which evaluated IV iron with the use of ESA included patients with serum ferritin values ranging from ≥ 100 ng/mL to ≤ 900 ng/mL.

[o] There is insufficient data to consider IV iron as monotherapy for the treatment of functional iron deficiency anemia.

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INDICATIONS FOR RED BLOOD CELL TRANSFUSION IN CANCER PATIENTS

Goal: Prevent or treat deficit of oxygen-carrying capacity

Asymptomatic

- **Hemodynamically stable chronic anemia without acute coronary syndrome:**
  - **Transfusion goal to maintain hemoglobin 7 - 9 g/dL**

Symptomatic

- **Acute hemorrhage with evidence of hemodynamic instability or inadequate oxygen delivery:**
  - **Transfuse to correct hemodynamic instability and maintain adequate oxygen delivery**

- **Symptomatic (including tachycardia, tachypnea, postural hypotension) anemia (hemoglobin less than 10 g/dL):**
  - **Transfusion goal to maintain hemoglobin 8 - 10 g/dL as needed for prevention of symptoms**

- **Anemia in setting of acute coronary syndromes or acute myocardial infarction:**
  - **Transfusion goal to maintain hemoglobin ≥ 10 g/dL**

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (1 of 5)[1-4]

INITIAL DOSING

PACKAGE INSERT DOSING SCHEDULE

Epoetin alfa 150 units/kg 3 times wk by subcutaneous injection	→	Increase dose of epoetin alfa to 300 units/kg 3 times wk by subcutaneous injection
or		
Epoetin alfa 40,000 units every wk by subcutaneous injection	→	Increase dose of epoetin alfa to 60,000 units every wk by subcutaneous injection
or		
Darbepoetin alfa 2.25 mcg/kg every wk by subcutaneous injection	→	Increase darbepoetin alfa to up to 4.5 mcg/kg every wk by subcutaneous injection

or

Darbepoetin alfa 500 mcg every 3 wks by subcutaneous injection

ALTERNATIVE REGIMENS

Darbepoetin alfa 100 mcg fixed dose every wk by subcutaneous injection	→	Increase darbepoetin alfa to up to 150-200 mcg fixed dose every wk by subcutaneous injection[5]
or		
Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection[7]	→	Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection[6]
or		
Darbepoetin alfa 300 mcg fixed dose every 3 wks by subcutaneous injection	→	Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection[7]

or

Epoetin alfa 80,000 units every 2 wks by subcutaneous injection[8]

or

Epoetin alfa 120,000 units every 3 wks by subcutaneous injection[9]

TITRATION FOR NO RESPONSE

TITRATION FOR RESPONSE

- The dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.
- If Hb reaches a level needed to avoid transfusion or increases > 1 g/dL in any 2-week period, reduce dose by 25% for epoetin alfa and by 40% for darbepoetin alfa.

See Footnotes and References (ANEM- B 2 of 5)

See Erythropoietic Therapy-Adverse Effects (ANEM-B 3 of 5)

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 OF 5)

FOOTNOTES AND REFERENCES FOR 1 of 5

[1]The head to head comparisons of regimens are inconclusive with regard to superiority of one drug over another. Schwartzberg LS, Yee LK, Senecal, FM, et al. A randomized comparison of every-2 week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic. The Oncologist 2004;9:696-707. Waltzman R, Croot C, Justice G, et al. Randomized comparison of epoetin alfa (40 000 U weekly) and darbepoetin alfa (200 mcg every 2 weeks) in anemic patients with cancer receiving chemotherapy. Oncologist 2005;10:642-650.

[2]Less frequent dosing regimens could be considered as an alternative to dose reduction.

[3]The dosages and regimens included in this table have been evaluated in cancer patients receiving chemotherapy.

[4]IV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. (See manuscript for detailed discussion.) See Parenteral Iron Preparations (ANEM-E).

[5] Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst 2002;94:1211-1220.

[6]Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naïve patients and patients switched from epoetin alfa. Pharmacotherapy 2004;24:313-323.

[7]Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every 3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 2006;98:273-284.

[8]Henry DH, Gordan LN, Charu V, et al. Randomized, open-label comparison of epoetin alfa extended dosing (80 000 U Q2W) vs weekly dosing (40 000 U QW) in patients with chemotherapy-induced anemia. Curr Med Res Opin 2006;22:1403-1413.

[9]Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. J Clin Oncol 2006;24:1079-1089.

See Erythropoietic Therapy - Dosing and Titration (ANEM-B 1 of 5)

See Erythropoietic Therapy- Adverse Effects (ANEM-B 3 of 5)

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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 OF 5)

Cancer Patient Survival

- Studies have reported possible decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia and target hemoglobin levels of >12 g/dL.[1-8] One analysis in patients with cancer not receiving active therapy found decreased survival in ESA treated patients.[6] Please refer to the FDA website for additional information: http://www.fda.gov/cder/drug/infopage/RHE/default.htm. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa) to patients outside of the treatment period of cancer-related chemotherapy. A treatment period is defined as anemia following initiation of therapy and continuing approximately 6 weeks after the completion of treatment.
- While three meta-analysis updates on survival have indicated an increased mortality risk with the use of ESAs,[9,10,11,12] two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.[13,14]
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target hemoglobin of < 12 g/dL.
- Additional prospective clinical trials designed and powered to measure cancer patient survival are ongoing to provide clinicians with data to guide optimal use of erythropoietic agents.
- Because of the above issues, providers should inform patients of risks and benefits of ESA therapy versus red blood cell transfusion. (See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion - ANEM-D).

Thrombosis

- Early trials of recombinant human erythropoietin reported that a high target hematocrit (42 ± 3%) was found to have an increased number of vascular events (arterial and venous).
- Erythropoietin has a thrombogenic potential independent of hemoglobin levels.[15] Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. (See NCCN Venous Thromboembolic Disease Guidelines)
- A meta-analysis update on thrombotic complications confirms an increased thrombosis risk in cancer patients with use of erythropoietic agents.[9]
- A clinical trial in chronic kidney disease patients demonstrated an increased risk of stroke with darbepoetin alfa.[16]

Erythropoietic Therapy - Adverse Effects continued (ANEM-B 4 of 5)

See References (ANEM- B 5 of 5)

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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (4 OF 5)

Hypertension/seizures

- Blood pressure should be controlled in all patients prior to initiating therapy with erythropoietic drugs and must be monitored regularly in treated patients.
- Seizures have been reported in chronic renal failure patients receiving erythropoietic drugs.
- Hemoglobin level should be monitored to decrease the risk of hypertension and seizures. (See Titration for Response ANEM-B 1 of 5)

ESA Neutralizing Antibodies (Pure red cell aplasia-PRCA)

- Between 1998-2004, 197 cases of PRCA were reported in patients treated with erythropoietin.[17] Over 90% of these cases occurred with Eprex, an epoetin alfa product used outside of the United States. Patients who develop a loss of response to erythropoietic drugs should be evaluated for possible PRCA, and if present, all erythropoietic drugs should be discontinued.[18]
- In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia.[19] Since 2005, FDA safety databases have included information on 30 new cases of antibody-associated PRCA, primarily associated with subcutaneous administration of epoetin alfa and darbepoetin alfa.[20] This interpretation resulted in a class label change for all ESAs. The toxicity has been reported predominantly in patients with chronic renal failure receiving ESAs by subcutaneous administration. Any patient who develops a sudden loss of response to an ESA, accompanied by a severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, ESAs should be withheld and plasma should be sent for evaluation of assays for binding and neutralizing antibodies. ESAs should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESA products as antibodies may cross-react.

See References
(ANEM- B 5 of 5)

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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (5 OF 5)

ADVERSE EFFECTS REFERENCES

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Note: All recommendations are category 2A unless otherwise indicated.
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REMS: RISK EVALUATION AND MITIGATION STRATEGY FOR ERYTHROPOIESIS STIMULATING AGENTS (ESAs)[1]

The FDA requires that Erythropoiesis-Stimulating Agents (ESAs) be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy (REMS), to ensure the safe use of these drugs.

As part of the REMS, a Medication Guide explaining the risks and benefits of ESAs must be provided to all patients receiving ESAs. See Epoetin Alfa Medication Guide and See Darbepoetin Alfa Medication Guide.

In addition to the Medication Guide, healthcare professionals who prescribe ESAs to patients with cancer are required to enroll in the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology program.

- **Patients with cancer using ESAs should:**
  - **Understand the risks associated with use of ESAs. These risks include:**
    - **ESAs may cause tumors to grow faster.**
    - **ESAs may cause some patients to die sooner.**
    - **ESAs may cause some patients to develop blood clots, and serious heart problems such as a heart attack, heart failure or stroke.**
  - **Be aware that their healthcare professional has received special training about the use of ESAs in patients with cancer.**
  - **Read the Medication Guide to understand the benefits and risks of using an ESA.**
  - **Talk with their healthcare professional about any questions they may have about using ESAs.**
  - **Be aware that they will be asked to sign an acknowledgment form that says they have talked with their healthcare professional about the risks of ESAs. This form must be signed before patients begin a course of treatment with an ESA.**

Selected safety information for healthcare providers:[2]

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.**
- **To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.**
- **Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.**
- **Discontinue ESA therapy following the completion of a chemotherapy course when anemia resolves (usually 6-8 weeks after the last cycle).**

[1] Adapted from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm
[2] Selected safety information: https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp#isi

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COMPARISON OF RISKS AND BENEFITS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION[1]

ESA in the Cancer Setting		Red Blood Cell Transfusion	
Risks	• Increased thrombotic events • Decreased survival • Time to tumor progression shortened	**Risks**	• Transfusion reactions (hemolytic, febrile, non-hemolytic, lung injury, etc.) • Congestive heart failure • Virus transmission (hepatitis, HIV, etc.) • Bacterial contamination • Iron overload • Increased thrombotic events
Benefits	• Transfusion avoidance • Gradual improvement in fatigue	**Benefits**	• Rapid increase of hemoglobin and hematocrit levels • Rapid improvement in fatigue

[1] See the manuscript for detailed information regarding the risks and benefits of ESA use and red blood cell transfusion.

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PARENTERAL IRON PREPARATIONS[1-6] (1 of 3)

- **Parenteral Iron Preparations**
  - **Iron dextran**
  - **Ferric gluconate**
  - **Iron sucrose**
- **These products are helpful in treating iron deficiency in patients intolerant or unresponsive to oral iron therapy, and in treating functional iron deficiency as seen in chronic renal failure patients, and cancer patients who are receiving ESAs.**
- **Test doses are required for iron dextran, and strongly recommended for patients receiving ferric gluconate or iron sucrose who are sensitive to iron dextran or who have other drug allergies.**
- **Most adverse events associated with iron dextran occur with high molecular weight iron dextran (Dexferrum®).[7]**
- **The recommended iron dextran product is low molecular weight iron dextran (INFed®).[8]**
- **Patients with active infection should not receive IV iron therapy.**

See Recommendations for Administering Parenteral Iron Products (ANEM-E 2 of 3)

See References (ANEM-E 3 of 3)

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RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS[1-6] (2 of 3)

	Iron Dextran†	Ferric gluconate†	Iron sucrose†
Test dose	Required 25 mg slow IV push and wait 1 hr before giving main dose	MD discretion 25 mg slow IV push or infusion	MD discretion 25 mg slow IV push
Dosage[9]	100 mg IV over 5 min • Repeated dosing once weekly for 10 doses to achieve total dose of 1 g or • Total dose infusion given over several hours*	125 mg IV over 60 min • Repeated dosing given once weekly for 8 doses or 200 mg IV over 3-4 hrs • Repeated every 3 weeks for 5 doses • Individual doses above 200 mg are not recommended[10] • Maximum total dose = 1000 mg	200 mg IV over 60 min • Repeated dosing given every 2-3 weeks or 200 mg IV over 2-5 min • Repeated dosing given every 1- 4 weeks • Individual doses above 300 mg are not recommended[11] • Maximum total dose = 1000 mg
Routes	IV infusion IM (INFed®) (not recommended)	IV injection/infusion	IV injection/infusion

†Examples of adverse events associated with FDA approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritis, headaches, and dizziness.

*Dose = 0.0442 (Desired Hgb - Observed Hgb) X LBW + (0.26 X LBW). LBW = Lean Body Weight
If dose exceeds 1000 mg, remaining dose may be given after 4 wks if inadequate hemoglobin response.

See References (ANEM- E 3 of 3)

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RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS[1-6] (3 of 3)

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Anemia is prevalent in 30% to 90% of cancer patients.[1] Correction of anemia can be achieved by either treating the underlying etiology or providing supportive care by transfusion with packed red blood cells (PRBC) or administration of erythropoiesis-stimulating agents (ESAs), with or without iron supplementation. Recent studies demonstrating detrimental health effects of ESAs sparked a series of FDA label revisions and a sea change in the perception of these once commonly used agents. In light of this, the NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines underwent substantial revisions this year. The purpose of these NCCN Guidelines is two-fold: 1) to operationalize the evaluation and treatment of anemia in adult cancer patients, with an emphasis on those patients with anemia who are receiving concomitant chemotherapy, and 2) to enable the patient and clinician to assess anemia treatment options based upon the individual patient condition.

The pathophysiologic origins of anemia can be grouped into three categories: 1) decreased production of functional red blood cells (RBC), 2) increased destruction of RBCs, and 3) blood loss. Hence, anemia is characterized by a decrease in hemoglobin concentration, RBC count or packed cell volume to subnormal levels. An anemia scale by grade is provided by the National Cancer Institute (NCI) (Table 1).

Table 1. NCI Anemia Scale (Hemoglobin Level in g/dL)

Grade	Scale
1 (mild)	10 – lower limit of normal (LLN)
2 (moderate)	8 – <10
3 (severe)	6.5 – <8
4 (life-threatening)	life-threatening
5 (death)	death

Source: Adapted from the Common Terminology Criteria for Adverse Events. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Etiology

Causes of anemia in cancer patients are often multifactorial, adding to the complexity of the problem in evaluation. Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, hereditary disease, renal insufficiency, nutritional deficiencies, anemia of chronic disease, or a combination of these.[2, 3] The malignancy itself can lead to or exacerbate anemia in a number of ways.[4] Cancer cells may directly suppress hematopoiesis through bone marrow infiltration. They may produce cytokines that lead to iron sequestration which decreases RBC production and may even shorten survival. Chronic blood loss at tumor

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sites and organ damage can further exacerbate anemia from cancer. Additional indirect effects may include nutritional deficiencies caused by loss of appetite in the cancer patient, hemolysis by immune-mediated antibodies, or changes in coagulation capability. For these myriad of reasons, anemia is prevalent among cancer patients at initial presentation. For example, 32% of non-Hodgkin's lymphoma patients have anemia at diagnosis,[5] while 49% of patients are anemic when diagnosed with gynecological cancer.[6] In addition, the myelosuppressive effect of chemotherapy is a significant contributing factor to anemia for patients undergoing cytotoxic treatment.[7] Radiation therapy to the skeleton is also associated with hematologic toxicity. In a retrospective analysis, approximately one-third of 210 patients undergoing radiotherapy to the cranium and/or spine for treatment of primary tumors of the central nervous system developed grades 3 and 4 hematologic side effects.[8]

Anemia associated with myelosuppressive chemotherapy.
Chemotherapeutic agents induce anemia by directly impairing hematopoiesis, including synthesis of RBC precursors, in the bone marrow.[4] In addition, nephrotoxic effects of particular cytotoxic agents (eg, platinum-containing agents) can also lead to anemia through decreased production of erythropoietin by the kidney.[4]

Studies have identified patients with lung cancer and gynecologic malignancies as having a very high incidence of chemotherapy-induced anemia.[6, 7] Platinum-based regimens, commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to combined bone marrow and kidney toxicity.[7] Selected single agents and regimens frequently associated with anemia for different types of cancers taken from the 1999 review by Groopman and Itri are summarized in Table 2. It is important to note that the hematologic toxicities of newer cytotoxic agents, regimens and schedules are not reflected in this list, and a greater risk of anemia may potentially be associated with some of the more intensive chemotherapy regimens.[7]

The myelosuppressive effects of particular cytotoxic agents are likely to accumulate over the course of repeated cycles of therapy, resulting in a steady increase in the rate of anemia with additional chemotherapy cycles. For example, for patients in the European Cancer Anemia Survey (ECAS)[6], the rate of anemia (hemoglobin level < 12 g/dL) was found to increase from 19.5% in cycle 1 to 46.7% by cycle 5. An increase in the fraction of grades 2-3 anemia was also associated with a greater number of chemotherapy cycles. Other factors for consideration when evaluating risk of chemotherapy-induced anemia include the nadir hemoglobin level, the time to the nadir hemoglobin level (roughly estimated at 2 weeks, but time can vary), and whether a hemoglobin measurement is considered to be pre- or post-nadir.[4]

Guideline overview

The revised NCCN Guidelines start with an evaluation of anemia to delineate the etiology. This is followed by a risk assessment to determine the initial intervention plan. Special categories are outlined in considering the use of ESAs for long-term management. Further guidelines are provided on transfusion, erythropoietic therapy, as well as iron supplementation.

This guidelines algorithm is mainly focused on patients with solid tumors and chronic lymphoid malignancies. For anemia associated with myelodysplastic syndromes, myeloid malignancies, and acute lymphoblastic leukemia, clinicians are referred to relevant guidelines from the NCCN Guidelines Table of Contents. Blood and marrow stem cell transplant-related anemia is not addressed in these guidelines.

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Table 2. Incidence of anemia associated with chemotherapeutic agents and regimens.

Agent	Grade 1/2 (%) *	Grade 3/4 (%) *	Cancer
Cisplatin	NR	11	H & N
Docetaxel	73 - 85	2 - 10	NSCLC
	58 - 60	27 - 42	Ovarian
5-FU	NR	11	H & N
	50 - 54	5 - 8	Colorectal
Paclitaxel	93	7	Breast
Topotecan	NR	32	SCLC
	67	32	Ovarian
Vinorelbine	67 - 71	5 - 14	Breast
Regimen			
Cisplatin - cyclophosphamide	43	9	Ovarian
Cisplatin - etoposide	59	16 - 55	SCLC
VIP	NR	52	SCLC
5-FU - carboplatin	42	14	H & N
CHOP	49	17	NHL
Paclitaxel - doxorubicin	78 - 84	8 - 11	Breast
Paclitaxel - carboplatin	10 - 59	5 - 34	NSCLC

NR = not reported; H&N = head and neck cancer; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; NHL = non Hodgkin's lymphoma; 5-FU = 5-fluorouracil; VIP = etoposide – ifosfamide – cisplatin; CHOP = cyclophosphamide – doxorubicin – vincristine – prednisone.

* WHO or NCI scales.

Source: Adapted from Groopman JE, Itri LM, JNCI 1999;91:1616-1634.

Screening Evaluation

Given the wide variation in the hemoglobin level among healthy subjects, a universal "normal" value remains elusive. For cancer patients, NCCN Panelists are in agreement that a hemoglobin level of 11 g/dL or below should prompt evaluation of anemia. For patients with a high baseline level, a drop of 2 g/dL or more is also cause for concern and assessment. As discussed above, a cancer patient may suffer from anemia as the result of a combination of causes, some of which may not be directly related to cancer. The overall goals of evaluation are to characterize the anemia and identify any underlying comorbidity that can be potentially corrected.

Initial assessment

Initial broad characterization involves a complete blood count (CBC) with indices that will reveal if other cytopenias are present. A visual review of the peripheral blood smear is critical to confirm the size, shape, and color of RBCs. A detailed history and physical exam must be taken. The history should include the duration and time of onset of symptoms, comorbidities, family history, as well as exposure to antineoplastic drugs and radiation. Common complaints are syncope, exercise dyspnea, headache, vertigo, chest pain, fatigue (disruptive to work and daily activities), and abnormal menstruation in female patients. Pallor may be apparent. Cancer-related fatigue is defined in the NCCN Guidelines as "a distressing persistent subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with normal functioning" (see NCCN Cancer-Related Fatigue Guidelines). A key characteristic distinguishing fatigue related to cancer from fatigue in healthy individuals is that it is less likely to be ameliorated by rest.[9] The above clinical manifestations are neither sensitive nor specific to the type of anemia. Clinicians should watch out for signs of underlying etiologies such as jaundice, splenic enlargement, neurologic symptoms, blood in stool, petechiae, heart murmur, among others.

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Approaches to evaluation

There are two common approaches to evaluating anemia: morphologic and kinetic. A complete evaluation often utilizes both. The morphologic approach is a characterization of anemia by the mean corpuscular volume (MCV), or average RBC size, reported in the initial CBC test:

- Microcytic (< 80 fL) – most commonly caused by iron deficiency; other etiologies include thalassemia, anemia of chronic disease, and sideroblastic anemia.
- Macrocytic (> 100 fL) – the majority of which is megaloblastic, pointing towards B12 or folate deficiency caused by insufficient uptake or inadequate absorption through lack of intrinsic factor. Non-megaloblastic anemia is less common and may be the result of alcoholism. Myelodysplastic syndrome and certain drugs such as hydroxyurea or diphenytoin can also cause macrocytosis.
- Normocytic (80-100 fL) – may be due to hemorrhage, hemolysis, bone marrow failure, anemia of chronic inflammation or renal insufficiency. The key follow-up test is the reticulocyte count (see below).

The kinetic approach focuses on the underlying mechanism of anemia, distinguishing among the production, destruction and loss of RBCs. The main starting point is the reticulocyte count corrected against the degree of anemia (reticulocyte index, RI), a measurement of the fraction of reticulocytes (immature RBC) in blood that provides an indication of the RBC production capacity by the bone marrow. The normal RI ranges between 1.0 and 2.0.

- Low RI – indicates decreased RBC production, suggesting iron deficiency, B12/folate deficiency, aplastic anemia, or bone marrow dysfunction due to cancer or cancer-related therapy (radiation or myelosuppressive chemotherapy).
- High RI – indicates normal or increased RBC production, suggesting blood loss or hemolysis in the anemic patient.

A comprehensive review to the follow-up and treatment of each subtype of anemia related to causes independent of myelosuppressive cancer therapy is beyond the scope of this guideline. Below is a summary of additional cues or tests for common underlying ailments:

- Absolute iron deficiency – iron and total iron binding capacity (TIBC) resulting in transferrin saturation < 15%, ferritin < 30 ng/mL (Functional iron deficiency is discussed within the context of ESA therapy in a later section)
- B12/folate deficiency – low vitamin B12 or folate levels
- Hemorrhage – stool guaiac positive, endoscopy findings
- Hemolysis – Coombs test positive, disseminated intravascular coagulation (DIC) panel positive, low haptoglobin levels
- Kidney disease – glomerular filtration rate (GFR) < 60, low erythropoietin level
- Inherited anemia – personal and family history
- Sideroblastic anemia – sideroblasts present in bone marrow biopsy

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Any cause of anemia that may be rectified independent of cancer therapy should be treated as indicated. When no such etiology is identified, the effects of cancer-related inflammation or myelosuppressive chemotherapy (if applicable) should be considered as the cause of anemia in the cancer patient.

Risk Assessment

If the likely cause of anemia is cancer-related inflammation or myelosuppressive chemotherapy (for solid tumors or lymphoid malignancies), a risk assessment of the anemia is necessary to determine the initial intervention plan – whether the patient requires an immediate boost in hemoglobin levels by PBRC transfusion. Consideration of ESA therapy is generally a long-term management decision given its potential risks.

It is important to note that the decision to conduct PRBC transfusion should not be made strictly on the basis of whether the hemoglobin level of the patient has reached a certain threshold or "trigger". The NCCN Panel outlines three general categories: 1) asymptomatic without significant comorbidities, for which observation and periodic re-evaluation are appropriate; 2) asymptomatic with comorbidities or high risk, for which transfusion should be considered; and 3) symptomatic, for which patients should receive transfusion. The clinical manifestations of anemia are associated with the onset, severity, and duration of the anemia, as well as other factors influencing tissue demands for oxygen. When anemia onset is acute, symptoms are likely to be more pronounced, since physiologic adjustments to compensate for lower oxygen-carrying capacity of the blood can occur with gradual onset of anemia. These adaptive measures include heightened cardiac output, increased coronary flow, altered blood viscosity, and changes in oxygen consumption and extraction. The presence of preexisting cardiovascular, pulmonary, or cerebral vascular disease may compromise the ability of a patient to tolerate anemia. Hence, decisions related to whether immediate correction of anemia is needed must be based on an assessment of individual patient characteristics, degree of severity of anemia, presence and severity of comorbidities, and the clinical judgment of the physician. For example, even when an anemic patient has no physiological symptoms or significant comorbidity, transfusion may be appropriate if there is a progressive decline in hemoglobin level following anti-cancer treatment.

Red Blood Cell Transfusion

PRBCs are the blood product of choice for transfusion to correct anemia. These are concentrated from centrifuged whole blood donations or collected by apheresis. The component is anticoagulated and may contain added preservatives. Further enhancements include leuko-reductions, irradiation, freezing, and washing. Certain patients may especially need PRBCs that are cytomegalovirus (CMV) negative. One unit of PRBC (300 cc) can have a hematocrit ranging from 50-80%, and typically contains 42.5-80 g of hemoglobin (with 147-278 mg of iron) or 128-240 mL of pure RBCs.[10]

Benefits of transfusion

The major benefit of transfusion with PRBC, offered by no other treatment of anemia, is a rapid increase in hemoglobin and hematocrit levels. Hence, PRBC transfusion is the only intervention option for patients receiving myelosuppressive chemotherapy who require immediate correction of anemia. Transfusion of 1 unit (300 cc) of PBRC has been estimated to result in an average increase in hemoglobin level of 1 g/dL or hematocrit by 3% in a normal-size adult who is not experiencing a simultaneous loss of blood.[10, 11]

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Results of a number of studies evaluating the impact of transfusion on mortality in critically-ill patients have been conflicting, with some studies showing a survival benefit for patients receiving transfusion. For example, in a study of 56 consecutive patients with unresectable esophageal cancer receiving chemoradiation therapy, blood transfusion was associated with an increase in overall survival (hazard ratio=0.26; 95% CI, 0.09-0.75, P=0.01).[12]

Risks of transfusion

Risks associated with PRBC transfusion include transfusion-related reactions, congestive heart failure, bacterial contamination and viral infections, and iron overload (reviewed by Spivak, Gascon, and Ludwig[13]). Since 1984, the introduction of numerous safety interventions to screen the U.S. blood supply for infectious organisms has dramatically decreased the risk of transfusion-transmitted infections.[14, 15] Pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions, the most common adverse reaction.[16, 17] However, Khorana et al analyzed data from discharge summaries of cancer patients admitted to 60 US medical centers between 1995 and 2003 and found increased risks (P < 0.001) of venous thromboembolism (OR=1.60; 95% CI, 1.53-1.67), arterial thromboembolism (OR=1.53; 95% CI, 1.46-1.61) and mortality (OR=1.34; 95% CI, 1.29-1.38) associated with PRBC transfusions.[18]

The condition of transfusion-related iron overload is observed in patients requiring frequent transfusions over several years to manage their anemia (ie, patients with MDS).[19] However, iron overload is unlikely to occur in patients receiving transfusions that are restricted to the limited time period corresponding to chemotherapy treatment (usually < 1 year). Another factor for possible consideration in the context of full reliance on PRBC transfusion as a treatment for chemotherapy-induced anemia relates to the limited supply of blood in the U.S. A recent analysis which modeled the impact of reducing ESA use in this population indicated that approximately 202,000 additional units of PRBC would be required to treat anemia in patients undergoing chemotherapy if ESA use was reduced by 75%.[20]

Transfusion goals and basic principles

There is wide variation in reported RBC transfusion practice,[4, 14, 21] but institutional and clinical practice guidelines are often “restrictive” in that they are based on limiting exposure to allogeneic blood.[14] The overall goal of transfusion is to treat or prevent deficit of oxygen-carrying capacity in blood, in order to improve oxygen delivery to body tissues. Target hemoglobin ranges for specific conditions recommended by the NCCN panel are outlined in the algorithm (“Indications for Red Blood Cell Transfusion in Cancer Patients” section). Transfusion is rarely indicated when the hemoglobin level is above 10 g/dL. In the multi-center TRICC (Transfusion Requirements In Critical Care) trial of 838 critically ill patients, no significant in-hospital mortality differences were observed for patients randomly assigned to receive transfusions to maintain hemoglobin levels of 7-9 g/dL (restrictive strategy) versus 10-12 g/dL (liberal strategy).[22]

Prior to transfusion, PRBCs must be crossmatched to confirm compatibility with ABO and other antibodies in the recipient. Premedication (acetaminophen or antihistamine) is seldom required for patients for whom long-term transfusion is not planned. If repeated transfusions are required, leukocyte-reducing blood and use of premedication can minimize adverse transfusion reactions. In most instances, PRBCs should be transfused by the unit and reassessment should be conducted after each transfusion.

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Erythropoietic Therapy

RBC production is normally controlled by erythropoietin, a cytokine produced in the kidneys. First introduced in 1989, ESAs are synthetic, recombinant human erythropoietin that can stimulate erythropoiesis in patients with low RBC levels. At present, two ESAs are available in the U.S.: epoetin alfa and darbepoetin alfa. Unlike transfusion that almost immediately boost the hemoglobin level, ESAs can take weeks to initiate a hemoglobin response, but they are effective at maintaining a target hemoglobin level with repeated administration. Popularity of ESAs reached a peak in 2003 to 2004, when their use for cancer patients alone accounted for 17% of all Medicare Part B spending.[23] However, this paradigm is shifting dramatically as evidence of potential detrimental effects started to emerge in recent years (see below).

Benefits of ESA therapy

Avoidance of transfusion is the main benefit of ESAs. Administration of ESA therapy has been demonstrated to decrease PRBC transfusion requirements in cancer patients undergoing chemotherapy. In a randomized, placebo-controlled study by Littlewood and colleagues, epoetin alfa was shown to reduce transfusion requirements in patients with anemia receiving chemotherapy.[24] Transfusion requirements were significantly decreased in the epoetin arm compared with placebo (24.7% versus 39.5%, P = 0.0057), and rise in hemoglobin level was increased (2.2 g/dL versus 0.5 g/dL; P < 0.001).[24] A double blind, placebo-controlled, randomized phase III study of darbepoetin alfa enrolled 320 patients (hemoglobin level ≤ 11 g/dL) receiving darbepoetin alfa at 2.25 mcg/kg/week versus placebo.[25] Patients receiving darbepoetin alfa required fewer transfusions (27% vs. 52%; 95% CI, 14%-36%, *P* < 0.001) than patients receiving placebo. The ability of ESAs to reduce transfusions was one endpoint used in a Cochrane review of 42 randomized, controlled clinical trials involving use of ESA therapy which enrolled a total of 6,510 patients undergoing treatment for cancer.[26] A decreased relative risk for transfusion was observed in the patients receiving erythropoietin (RR=0.64; 95% CI, 0.60-0.68).

Risks of ESA therapy

Increased mortality and tumor progression. Starting from 2007, the FDA made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa,[27] including addition of a "Black Box" label warning[28] and implementation of a risk management program known as Risk Evaluation and Mitigation Strategy (REMS, see algorithm). The strengthened FDA restrictions were mainly based on the results of eight randomized studies that individually showed a decrease in overall survival and/or decreased loco-regional disease control with ESA usage for advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers.[29-36] Details of the studies and their outcomes are presented in Table 3. Of the eight studies, three investigated ESA effects in patients who underwent chemotherapy. All eight trials had an off-label target hemoglobin level of over 12 g/dL.

Worsened health outcomes associated with the use of ESAs have been confirmed in three recent meta-analyses of 51-53 randomized controlled trials.[37-40] Bohlius et al[38], Tonelli et al[39], and Bennet et al[37] each reported increased mortality in patients receiving ESAs with relative risks/hazard ratios of 1.17 (95% CI, 1.06-1.30), 1.15 (95% CI, 1.03-1.29), and 1.10 (95% CI, 1.01-1.20), respectively. However, this association has been refuted by two other meta-analyses reporting no significant effect of ESAs on mortality or progression.[41, 42] In addition, there are data from randomized studies that showed no increase in mortality with ESA use according to prescribing label specifically in patients receiving chemotherapy for small cell lung cancer (SCLC).[43-45]

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Table 3. Summary of randomized trials that showed adverse health effects with ESA.

Study/Tumor/(n)	ESA treatment, duration	Hb start value (g/dL)	Hb target value (g/dL)	Adverse Outcome
Chemotherapy				
PREPARE,[29] breast cancer, n=733	Darbepoetin alfa (4.5 µg/kg/2 wk), Not reported	Mean 13.6	≥13	Decreased OS, 14% vs 10% death; faster tumor growth
BEST,[32] metastatic breast cancer, n=939	Epoetin alfa (40 000 U/wk), 12 months	≤ 13	>14	Decreased 12-month survival, 70% vs 76%, P = 0.01
20000161,[30] lymphoid malignancy, n=344	Darbepoetin alfa (2.25 µg/kg/wk), 12 wk	≤11	≥14 (women) ≥15 (men)	Decreased OS, HR for death = 1.37, P = 0.04
Radiotherapy				
ENHANCE,[31] head and neck, n=351	Epoetin beta (300 IU/kg x 3/wk), 7-9 wk	<12 (women) <13 (men)	≥14 (women) ≥15 (men)	Decreased OS, HR for death = 1.39, P = 0.02; locoregional progression, HR = 1.69, P = 0.007
DAHANCA 10,[33] head and neck, n=522	Darbepoetin alfa (150 µg/wk), Terminated early	≤14.5	>15.5	Increased locoregional failure, RR = 1.44, P = 0.03
Chemoradiotherapy				
GOG-191,[35] cervical cancer, n=113	Darbepoetin alfa (40 000 U/wk), Terminated early	<12	>14	Decreased OS, 61% vs 75%; decreased PFS, 58% vs 65%
No therapy/palliative radiotherapy				
EPO-CAN-20,[36] non-small cell lung cancer, n=70	Epoetin alfa (40 000 U/wk), 12 wk	<12.1	>14	Decreased OS, HR for death = 1.84, P = 0.04
Amgen 103,[34] non-myeloid cancer, n=989	Darbepoetin alfa (6.75 µg/kg/4 wk), 16 wk	≤11	>13	Decreased OS, HR for death = 1.3, P = 0.008

Hb = hemoglobin; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

Source: adapted from Bennett et al, JAMA 299: 914-924, 2008.

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Risk of thromboembolism. Increased thromboembolic risks have been associated with ESA treatment of cancer patients. The cause of venous thromboembolism (VTE) is complex; a heightened baseline risk is related to the malignancy itself as well as chemotherapy (see NCCN Venous Thromboembolic Disease Guidelines). [46-49] Other risk factors for VTE in cancer patients include prior history of VTE, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents, prolonged inactivity by hospitalization, steroids, as well as comorbidities such as hypertension.[50]

Overall, results from meta-analyses established significant association: increased risk of thrombolic events with ESA usage was reported by Tonelli et al[39] (RR=1.69; 95% CI, 1.27-2.24), Bennett et al[37] (RR=1.57; 95% CI, 1.31-1.87), Ludwig et al[41] (HR = 1.57; 95% CI, 1.10-2.26), and Glaspy et al[42] (OR = 1.48; 95% CI, 1.28-1.72). A combined analysis of six trials on darbepoetin alfa by Glaspy and colleagues [51] also found an increased risk of thromboembolism for patients with hemoglobin > 12 g/dL (RR=1.66; 95% CI, 0.9-3.04) or patients achieving over 1 g/dL increase in 14 days (RR= 1.67; 95% CI, 0.96 -2.88). As well, an increased risk of stroke was associated with darbepoetin alfa in a clinical trial of patients with chronic kidney disease (HR = 1.92; 95% CI, 1.38-2.68).[52] The increased risk of thromboembolism in cancer patients receiving ESA therapy is specified in the black-box warnings included in the updated FDA labels. The NCCN panel cautions physicians to be alert of the signs and symptoms of thromboembolism in cancer patients receiving ESAs.

Risk of hypertension/seizures. Seizures have been reported in patients with chronic renal failure receiving ESAs. There is a 2.5% incidence of seizure in patients on dialysis during the first 90 days of therapy.[27] While it is unclear whether cancer patients receiving ESA therapy are at risk for seizures, hemoglobin levels should be monitored before and during the use of ESAs to decrease the risk of these adverse events.

Risk of pure red cell aplasia. Pure red cell aplasia (PRCA) is a rare syndrome of anemia characterized by a low reticulocyte count, a loss of bone marrow erythroblasts, neutralizing antibodies against erythropoietin, and resistance to ESA therapy. From 1998 to 2004, however, a marked rise in incidence (191 cases) was observed, 90% of which occurred with Eprex®, an epoetin alfa product used outside of the United States.[53, 54] Causation was attributed to formulations without human serum albumin, subcutaneous administration, and uncoated rubber stoppers.[55] Interventions designed accordingly reduced the incidence by 83%. In 2005, the FDA interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia, with or without other cytopenias, associated with neutralizing antibodies.[56] This resulted in a class label change for all ESAs. Toxicity has been reported predominantly in patients with chronic renal failure receiving subcutaneous ESAs.

The NCCN panel recommends that any cancer patient who develops a sudden loss of response to ESA, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect. ESAs should be withheld while plasma is sent to ESA-producing pharmaceutical companies for evaluation of assays for binding and neutralizing antibodies to erythropoietin. ESAs should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESA products as antibodies may cross-react.

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NCCN Recommendations

To promote safety, the FDA requires that ESAs only be administered with informed patient consent under the REMS program that consists of Medication Guides for patients and the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs) program for prescribing physicians (see “REMS” section of algorithm).

For cancer patients, the black-box warning on the revised FDA label states that ESAs should only be used to treat chemotherapy-induced anemia and should be discontinued once the chemotherapy course is complete.[28] Hence patients not receiving concomitant myelosuppressive chemotherapy are not eligible. As discussed above, randomized trial data suggest that ESAs may promote tumor growth in an off-target manner. For this reason, these agents should not be used when the anticipated treatment outcome is cure. These include primary and adjuvant chemotherapy for malignancies such as early-stage breast cancer and NSCLC, lymphomas, testicular cancer, among others. An exception to this may be SCLC, for which there are trials demonstrating no negative impact on survival or disease progression (see above). For patients undergoing palliative treatment, ESA therapy can be considered preferentially over transfusion. The NCCN guidelines panel recognized that it is not always clear whether a chemotherapy regimen is considered curative. Under these circumstances, given that no other cause of anemia has been identified, the order of priority for anemia management should be: consideration of RBC transfusion, clinical trial enrollment if available, and lastly consideration of ESAs. Upon decision of ESA use, physicians were advised to use the lowest dose necessary to avoid transfusion.

Chronic kidney disease (CKD) is an independent indication for ESA therapy. Risks of ESAs in these patients appear to be associated with high doses and/or high target hemoglobin levels, and the FDA label mandate individualized dosing to maintain hemoglobin levels between 10 and 12 g/dL. Since almost one-third of patients with end-stage renal disease are also inflicted with cancer, these represent a unique group that require personalized use of ESAs based on very careful weighing of risks and benefits (reviewed by Bennett et al[57]). For example, CKD patients not receiving active therapy for a malignancy should try to avoid ESAs, while those receiving palliative chemotherapy may favor ESAs over transfusions to treat severe anemia by carefully dosing for target hemoglobin between 10 g/dL and 12 g/dL in keeping with the indication for CKD. In the scenario where the CKD patient has a curable solid tumor, ESAs should not be administered during chemotherapy, but may be used with caution after chemotherapy is complete, keeping in mind the possibility of residual disease. Risk of thrombosis must be taken into account in weighing the risk-benefit ratio.

Iron studies should accompany ESA therapy to monitor the development of functional iron deficiency (see below). These include serum iron, TIBC, and serum ferritin.

Dosing schedules

Epoetin alfa and darbepoetin alfa are considered equivalent by the NCCN panel. Recommended initial dosing schedules for patients receiving chemotherapy are summarized in the algorithm. The most common initial dosing schedules for epoetin alfa evaluated in clinical trials of cancer patients are 150 units/kg three times weekly administered subcutaneously [24, 58] and 40,000 units once weekly SC. [32, 35, 36, 59] Both of these initial dose schedules are currently recommended. Other dosing ranges and schedules of epoetin alfa may be considered, including an extended dosing of 80,000 U SC every 2 weeks[60] and a dose of 120,000 U SC once every 3 weeks.[61]

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Although darbepoetin doses were initially administered at 2.25 mcg/kg SC every week,[25, 30, 62] there has been interest in using fixed doses and higher doses at decreased frequency. A randomized trial compared weekly dosing at 2.25 mcg/kg vs. fixed dosing at 500 mcg every three weeks in 705 patients with non-myeloid malignancies with a hemoglobin level <11 g/dL. The percentage of patients achieving the target hemoglobin level (≥11 g/dL) was 77% in the weekly arm and 84% for patients receiving darbepoetin alfa every three weeks.[62] Currently the NCCN panel recommends both schedules. A number of studies have demonstrated the safety and efficacy of alternative dosing schedules for darbepoetin alfa. These include a fixed weekly dose of 100 mcg,[25] a fixed dose of 200 mcg biweekly,[63] and 300 mcg every 3 weeks.[64]

Response assessment and dose titration

Response to ESA therapy is assessed to determine whether the initial dose should be reduced, escalated, or withheld. Decisions related to ESA dose adjustment are based on the goal of a gradual increase in hemoglobin level to avoid transfusion.

ESAs require at least 2 weeks of treatment before there is an increase in the number of RBCs. Hemoglobin levels should be measured weekly until they stabilize. Dose reduction should be implemented if the hemoglobin level increases by 1 g/dL or more during a 2-week period, or if hemoglobin reaches a level sufficient to avoid transfusion. Doses of epoetin alfa and darbepoetin alfa should be decreased by 25% to 40%, although individualized dose titrations may be needed.

Conversely, the ESA dose should be increased according to the algorithm (see “Erythropoietic therapy – Dosing and titration”) for patients receiving chemotherapy who show no response (less than 1 g/dL in hemoglobin increase) in hemoglobin level following 4 weeks of epoetin alfa or 6 weeks of darbepoetin alfa. Iron supplementation can be considered to improve response to ESA therapy (see below). A subsequent response at 8 or 9 weeks for patients on ESA dosing schedules of every 2 or 3 weeks may necessitate a dose titration with the goal to avoid transfusion. Individuals receiving weekly doses of ESA therapy can be evaluated for subsequent response at 8 or 9 weeks. The same dose reduction formulas as described above should be followed. ESA therapy should be discontinued in patients showing no response despite iron supplementation after 8 or 9 weeks of therapy, and PRBC transfusion should be considered. ESAs should be discontinued when chemotherapy is complete and anemia has resolved, usually within 6 weeks.

Iron Monitoring and Supplementation

“Functional” iron deficiency often arises following continued erythropoietin use, and iron supplementation will eventually be required in most patients to maintain optimal erythropoiesis.[65, 66] This is because rapid ESA-stimulated RBC production can surpass the rate of iron stabilization from stores to the usable iron pool in the reticuloendothelial system. Release of iron can be further delayed by inflammatory cytokines released in the tumor setting. The overall result is a blunted erythropoietin response to anemia. If the patient is to receive erythropoietic therapy, additional iron studies, including serum iron, TIBC, and serum ferritin should be performed prior to treatment, in order to rule out absolute iron deficiency which may respond to oral iron therapy.

Iron can be administered in oral form or parenteral form (low-molecular weight iron dextran, ferric gluconate, and iron sucrose). Evidence from five published studies suggests that IV iron is superior to oral iron. Patients participating in these trials had serum ferritin levels ranging

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from ≥ 100 ng/mL to ≤ 900 ng/mL. A prospective, multicenter, open-label trial randomized 157 patients with chemotherapy-induced anemia receiving epoetin alfa to (1) no iron, (2) oral iron, (3) iron dextran IV bolus, (4) iron dextran total dose infusion.[67] Increases in hemoglobin levels were greater with IV iron (groups 3 and 4) compared to oral supplementation or no iron (P < 0.02) while there was no difference between the oral and no iron groups (P = 0.21). In a second open-label study by Henry and colleagues,[68] 187 anemic cancer patients receiving chemotherapy and epoetin alfa were randomized to no iron, oral ferrous sulfate three times daily, or weekly IV ferric gluconate. IV iron produced a significantly greater hemoglobin response than oral or no iron. Response rate was also higher in the IV arm (73%) compared to oral (45%) or no iron (41%). A third study was conducted on 67 patients with lymphoproliferative malignancies not undergoing chemotherapy.[69] Patients were randomized to weekly epoetin beta with or without IV iron sucrose. Although an oral iron arm was not included, IV iron resulted both in higher mean change in hemoglobin level from baseline (2.76 g/dL versus 1.56 g/dL, P= 0.0002) and in a higher hemoglobin level response rate (87% versus 53%, P = 0.0014) compared to the no-iron group.

Two additional studies were published in 2008. Bastit et al reported their open-label trial on 396 patients with nonmyeloid malignancies undergoing chemotherapy (hemoglobin level less than 11 g/dL).[70] These were treated with darbepoetin alfa with or without IV iron (iron sucrose or ferric gluconate) every three weeks for 16 weeks. Again, hematopoietic responses and time to reach target hemoglobin level was improved in the IV iron arm. Most significantly, this is the first study to associate IV iron with fewer RBC transfusions (9% versus 20%, P = 0.005). In a study by Pedrazzoli et al,[71] 149 patients with solid tumors and chemotherapy-induced anemia were randomly assigned to weekly darbepoetin alfa with or without ferric gluconate. This is the first trial that excluded patients with absolute or functional iron deficiency; eligibility requirements included serum ferritin levels greater than 100 ng/ml and TSATs greater than 20%. The ESA/IV iron group showed a higher hematopoietic response rate (93% versus 70%, P = 0.0033) compared to the control group. These studies demonstrated that concurrent IV iron may enhance hematologic response to ESAs, although there is insufficient evidence to determine whether iron supplementation can allow an ESA dose decrease. Long-term effects of IV iron supplementation had not been assessed in these five trials.

In 2009, Steensma et al reported findings from the largest trial to date that challenged results from the above studies.[72] About 500 patients receiving chemotherapy were randomized 1:1:1 to IV ferric gluconate, oral ferrous sulfate, or oral placebo. IV iron failed to confer any benefit in terms of hemoglobin response, transfusion rates, or quality of life, but was associated with significantly more grade 3 or 4 adverse events compared to oral iron and placebo (54%, 43%, 45%, respectively; P = 0.03). The reason for this discordance remains unclear.

NCCN Recommendations

In the NCCN guidelines, IV iron products are recommended for iron repletion in cancer patients with absolute iron deficiency (ferritin < 30 ng/mL and transferrin saturation < 15%). It can also be considered in combination with erythropoietic drugs for patients with functional iron deficiency ferritin ≤ 800 ng/mL and transferrin saturation < 20%). Common adverse events following FDA approved doses of parenteral iron include hypotension, nausea, vomiting and/or diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness.[73-75] Most adverse events associated with iron dextran occur with high molecular weight iron dextran (Dexferrum®).[76] The recommended iron dextran product is low molecular weight iron dextran (INFed®).[77] Test doses are

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required for iron dextran, and strongly recommended for patients receiving ferric gluconate or iron sucrose who are sensitive to iron dextran or who have other drug allergies. Dosage details for administering parenteral iron therapy are listed in the algorithm (see "Recommendations for administering parenteral iron products"). Although data are conflicting in literature, concerns exist regarding IV iron possibly promoting inflammation and bacterial growth.[78] Hence iron supplementation is not recommended for patients with active infection.

Future Development

In the face of current controversy in various aspects of anemia management, well-designed trials are required to answer questions regarding the safety of ESAs for lower target hemoglobin levels, the role of IV iron in reducing transfusion needs, long term effects of iron supplementation, among others.

Several novel agents haven been demonstrated to improve anemia in non-cancer settings.[79] Examples are continuous erythropoietin receptor activator (CERA)[80, 81] and the peptide-based erythropoietin-receptor agonist peginesatide.[82] Their value in treating anemia among the cancer population requires further study.

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